Cardiology and Angiology: An International Journal

Volume 13, Issue 3, Page 67-80, 2024; Article no.CA.117946
ISSN: 2347-520X, NLM ID: 101658392

Anti-cancer Therapies in Adults and Their Effects on Cardiovascular System: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ca/2024/v13i3426

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/117946

Original Research Article

Received: 15/04/2024
Accepted: 21/06/2024
Published: 26/06/2024

ABSTRACT

The cardio-oncology as a field has been expanded by the rapid development of innovative cancer therapies. While these treatments had significantly improved the overall survival rates for cancer patients, they also carried the risk of cardiovascular and metabolic toxicities. A comprehensive and accurate diagnosis of cancer was paramount to initiate appropriate and effective treatment strategies. It was essential to recognize that each type of cancer presents unique characteristics and complexities, necessitating personalized treatment approaches tailored to individual patients. These treatment regimens often encompassed a combination of modalities such as surgery, radiotherapy, systemic therapy, including chemotherapy, antineoplastic hormonal agents, targeted therapies, and supportive care interventions. By implementing a tailored treatment plan based on the specific nature of the cancer, healthcare professionals might optimize therapeutic outcomes while minimizing adverse effects, ultimately improving the overall prognosis and quality of

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Cite as: *Habbal, Rachida, Saadia Ouarrak, and Hind Dehbi. 2024. "Anti-Cancer Therapies in Adults and Their Effects on Cardiovascular System: A Review". Cardiology and Angiology: An International Journal 13 (3):67-80. https://doi.org/10.9734/ca/2024/v13i3426.*

life for cancer patients. The concise review aims to underscore the effects of cancer and its treatments on cardiovascular health, drawing insights from prior research. By synthesizing findings from existing studies, we aim to elucidate the intricate relationship between cancer therapies and cardiovascular outcomes. Consequently, there is a pressing need for an updated summary to inform contemporary clinical practice, ensuring that healthcare professionals are equipped with the latest knowledge to provide optimal care for cancer patients while safeguarding their cardiovascular well-being.

Keywords: Cardio-oncology; cardiotoxicity; neoplasms; heart disease; cardiovascular system.

1. INTRODUCTION

A thorough diagnosis of cancer is crucial for administering tolerated and efficient treatment. Each type of cancer requires a tailored treatment plan. Typically, treatment comprises surgery, radiotherapy, and/or systemic therapy (chemotherapy, antineoplastic hormonal drugs, targeted therapies, supportive care).

According to the latest World Health Organization (WHO) data, “cardiovascular diseases (CVD) were the leading cause of death globally. An estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths”. “The exact ranking of cancer among causes of death might vary depending on factors such as region, age, and socioeconomic status. However, cancer ranked among the top causes of death globally with almost 10 million deaths in 2020” [1].

Several common lifestyle factors contribute to the risk of developing both cancer and cardiovascular disease. Among these, smoking stands out as one of the most significant. Alcohol consumption is another lifestyle factor that affects both cancer and cardiovascular health. A sedentary lifestyle, exposure to pollution, whether outdoor air pollution or indoor pollutants such as secondhand smoke are shared risk factors for cancer and CVD. The most common in 2020, in terms of new cases of cancer, were breast with 2.26 million cases, then lung with 2.21 million cases, followed by colon and rectum with almost 1.93 million cases [2,3,4,5].

The mini review aims to highlight, based on previous studies, the impact of cancer and its therapies on the cardiovascular system. Hence, an updated summary is needed for guiding today's clinical practice.

2. METHODOLOGY

To conduct a targeted search on PubMed focusing on adults and articles published within the last five years, we employed MeSH terms and Boolean operators. Specifically, our search strategy included the following terms: (("Cardiotoxicity"[Mesh]) AND "Neoplasms "[Mesh]) NOT "Hematologic Neoplasms"[Mesh]. By incorporating MeSH terms and limiting the search to articles published within the past five years, we aimed to retrieve the most current and relevant literature. Additionally, to ensure relevance to our study population, we specified adults in our search criteria. Hematologic neoplasms were explicitly excluded from the search to maintain focus on non-hematologic malignancies.

3. RESULTS AND DISCUSSION

The different therapies discussed in this paper are for indicative purposes only. The list is not exhaustive. Other treatments might have a significant impact on the cardiovascular system.

3.1 Multidisciplinary Management

Cancer management was certainly multidisciplinary including, but not limited to, radiologists, biologists, surgeons, pathologists, oncologists, radiation oncologists, and cardiologists. The most suitable approach was based on discussion in multidisciplinary team according to each patient characteristics [6]. Several therapies and procedures might be proposed, e.g.:

- Chemotherapy: Anthracycline, fluoropyrimidine, cyclophosphamide, taxane,
- Targeted therapies: Trastuzumab (anti-Human Epidermal Growth HER 2), bevacizumab (anti- Vascular endothelial growth factor), tyrosine kinase inhibitors (Sunitinib, Osimertinib), cyclin-dependent kinase 4/6 inhibitors (Ribociclib)
- Antineoplastic hormonal agents:

- Tamoxifen, aromatase inhibitors

- Ovarian function suppression, Androgen deprivation therapy

- Immune checkpoint inhibitors

- Radiotherapy (mediastinal, left-sided breast cancer)

- Supportive care: corticosteroids, other medications (They were taken into account for drug-drug interaction)

Polypharmacy in cancer patients was limiting the use of medications that might interfere with cancer treatments to essential ones and closely monitoring their cardiovascular side effects and potential drug interactions. Additionally, electrolyte imbalances such as hypokalemia, and hypomagnesemia were frequently corrected. Indeed, during chemotherapy, there was often a volume increase due to intravenous fluids, which might affect cardiac function [7].

3.2 Patient Characteristics and Risk Stratification

Generally, cancer patients were of advanced age, with pre-existing comorbidities. Natural or induced menopause led to changes in lipid profiles, increased blood pressure, and alterations in vascular function, and was considered a cardiovascular risk factor [8]. In addition to sharing several risk factors with cardiovascular diseases, cancer predisposed individuals to thromboembolic disease due to production of pro-inflammatory cytokines and hypercoagulability in addition to endothelial dysfunction. Nevertheless, cancer predisposed to major bleeding especially in advanced tumors or during thrombocytopenia due to bone marrow invasion. Baseline risk stratification remained a crucial step before initiating any therapy, as it helped to determine the balance benefit/risk, as well as providing a reference for follow-up [9].

Several scores allowed physicians to assess the cardiovascular risk in general population, and a limited number of these were extrapolated to cancer patients. It helped to identify a mild, moderate, or high/very high-risk patients (e.g., Heart Failure Association-International Cardio-Oncology Society Risk Score (HFA-ICOS)) [10].

A baseline cardiovascular assessment has been performed via cardiac history, cancer treatment history, physical examination, blood pressure, electrocardiogram (ECG). Supplementary targeted exams, including an echocardiogram , blood tests (glycated hemoglobin (HbA1c), lipid profile, cardiac troponin, brain natriuretic peptide (BNP), or N-terminal pro-brain natriuretic peptide (NT-proBNP)), were required for initial risk stratification based on the planned therapy [9].

3.3 Chemotherapy

3.3.1 Anthracycline

“Chemotherapy was widely used in cancer management. Anthracycline-based regimens were commonly employed in breast cancer, which represented the most prevalent cancer in women worldwide” [11]. “The most known Anthracyclines was Doxorubicin and Epirubicin, acknowledged as a DNA intercalating agent. DNA was identified as the principal target for their pharmacological activity. No analog to date have shown an activity clearly superior to that of doxorubicin, which remained the best anthracycline in terms of efficiency” [12]. “A retrospective analysis of various clinical studies revealed that the onset of chronic cardiomyopathy was linked to the peak plasma concentration of Doxorubicin (Cmax). Similarly, in laboratory animals, this aligned with the ventricular peak following Doxorubicin administration and its major metabolites” [12]. “Anthracycline-induced cardiotoxicity has been understood to be a continuum that begins with subclinical myocardial injury and develops into asymptomatic left ventricular (LV) dysfunction and subsequent heart failure” [13]. “Further evidence that the cardiotoxicity of Doxorobucin correlated with its Cmax and diffusion into the heart came from the successful strategy of encapsulating the anthracycline molecule in liposomal delivery systems. Liposomal Doxorobucin reached high Cmax values and diffused through the discontinuous “leaky” endothelium of tumors; nevertheless, the liposomes were too large to permeate through the normal microvasculature of the heart” [12].

“Doxorubicin might damage the heart and its substructures in a dose-dependent manner, increasing the incidence of congestive heart failure by 4.7 %, 26 %, and 48 % at cumulative doses of 400, 550, and 700 mg/m2 of Doxorubicin, respectively” [14].

In addition to a baseline cardiovascular risk assessment before initiating anthracycline treatment, a special attention was required to the kinetics of various biological tests as well as the

variability of clinical and paraclinical examinations during treatment administration. Monitoring was scheduled based on the determined risk level: every 3 cycles for mild/moderate risk and before each cycle for high/very high risk. Treatment discontinuation was unavoidable in certain situations, and rediscussion of the overall management was performed within multidisciplinary team [7].

3.3.2 Fluoropyrimidine

“5-Fluorouracil (5-FU) and its oral prodrug Capecitabine belong to fluoropyrimidines. This chemotherapy was considered an anti-metabolite chemotherapy used to treat solid cancers, including gastrointestinal cancers, pancreatic cancer, breast cancer, and head and neck cancer. First, capecitabine was converted to 5′-deoxy-5-fluorocytidine by carboxylesterase, which was an enzyme located mainly in the liver. Second, 5′-deoxy-5-fluorocytidine was converted to 5′-deoxy-5-fluorouridine (5′-dFUR) by cytidine deaminase, which was mainly located in the liver and tumor tissue. Third, 5′-dFUR was converted to 5-FU by thymidine phosphorylase. Finally 80–90% of 5-FU was catabolized by dihydropyrimidine dehydrogenase (DPD) into metabolite 5-dihydrofluorouracil (5-FUH2), which was neither cytotoxic to the tumor cells nor toxic to normal cells” [15]. The DPD dosage was necessary, before each fluoropyrimidine administration, to predict potential toxicity.

The main observed cardiac event was chest pain. The theory suggesting vasospasm as the cause of myocardial ischemia has been proposed, as coronary angiography often didn’t reveal stenoses in patients experiencing acute 5-FU-induced cardiotoxicity [16–18]. Toxic myocarditis has been proposed by Sasson et al. as they found biventricular dilation and diffusely areas of cell necrosis associated with an inflammatory infiltrate, on autopsy of a case of 5-FU-induced fatal cardiogenic shock [19]. SCORE2/ SCORE2-OP or equivalent were recommended scores before starting fluoropyrimidines. The recommendation from the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice advocated for intensive management of modifiable cardiovascular risk factors both during and after treatment [20].

3.3.3 Cyclophosphamide

Cyclophosphamide demonstrated a bimodal mechanism of antitumor action, along with cardiotoxic and immunomodulatory effects. The variation in pharmacological effects was contingent upon the drug's metabolism and the dosing [21]. Cyclophosphamide and its metabolites, such as aldophosphamide, 4-hydroxy phosphamide, and acrolein, were recognized as cardiotoxic. Among these metabolites, acrolein was identified as the most cardiotoxic. Cardiomyocytes were highly sensitive to acrolein, a highly reactive aldehyde [22]. Another cardiotoxic mechanism of cyclophosphamide or its metabolite involved oxidative stress, nitrative stress, disrupted calcium homeostasis, which induced inflammation, apoptosis, swelling, nuclear splitting of cardiomyocytes, and alterations in signaling pathways such as NFkB, p53, and p38 MAPKs. These processes yielded cardiomyopathy, atrial fibrillation and heart failure [23].

3.3.4 Taxane

Taxanes were antineoplastic drugs that stabilize cellular microtubules. Paclitaxel and docetaxel were the most widely used in the carcinoma treatment. Signs of Taxane-induced cardiotoxicity encompassed left ventricular dysfunction, bradycardia, arrhythmias, and conduction disorders [24]. The risk of cardiotoxicity and probable allergic reactions imposed a close monitoring within and after taxane based chemotherapy [25]. In 5% of patients treated with paclitaxel, atrioventricular block, left bundle branch block, ventricular tachycardia, and ischemic cardiac events were observed [26]. The incidence of docetaxel-associated heart failure has been documented to range from 1.6 to 2% [27].

As the number of long-term survivors, elderly patients, and those with pre-existing cardiac risk factors increases, the toxicity profile of anthracyclines becomes a crucial factor in selecting adjuvant treatments. This concern is reflected in the significant use (47.8%) of anthracycline-free regimens, such as the combination of docetaxel and cyclophosphamide (TC), among older patients aged 67 to 94 years, as reported in a 2010 analysis of the SEER-Medicare database [28]. In the West German Study Group PlanB trial, six cycles of TC proved to be an effective and safe option for patients with human epidermal growth factor receptor 2 (HER2)–negative early breast cancer who had node negative (pN0) high genomic risk or pN1early breast cancer with intermediate- to high-risk genomic profiles [29].

3.4 Targeted Therapies

Targeted oncology included monoclonal antibodies, small molecule inhibitors, and antibody-drug conjugates. In the past decade, the U.S. Food and Drug Administration has approved approximately 40 new targeted therapies for 12 different cancers [30].

In targeted oncology, monoclonal antibodies were predominantly employed to target antigens on cancer cells, resulting in the downregulation of oncogene signaling pathways [31].

3.4.1 Monoclonal antibodies

3.4.1.1 Trastuzumab

Monoclonal antibodies targeting the human epidermal growth factor receptor 2 (HER2), such as trastuzumab, have significantly enhanced outcomes in HER2-positive breast cancer, a subtype that comprised 15% to 25% of all breast cancer patients. It was used in some advanced gastric adenocarcinoma. Trastuzumab binds to HER2 receptors on tumor cells, initiating internalization and downregulation of HER2 [32]. When anthracycline was indicated, either in localized disease or metastatic settings, it wasn't administered concurrently due to the potential additive toxicity [32]. Treatment with trastuzumab led to a reduction in myocyte contractility. Consequently, trastuzumab was less likely to be linked with myocyte death and was believed to induce temporary dysfunction, primarily reversible upon treatment cessation [33].

According to a published Cochrane review, in patients with early BC with high chance for cure, trastuzumab increased the risk of heart failure (HF) 5-fold and the left ventricular ejection fraction (LVEF) decline 2-fold [34].

For low risk patients undergoing neoadjuvant and/or adjuvant HER2-targeted therapies, echocardiography was performed every 3 months, with an additional assessment within 12 months following treatment completion [35].

3.4.1.2 Pertuzumab

Pertuzumab, another anti-HER2, that showed on the primary analysis of APHINITY, an improved invasive disease free survival in the adjuvant setting for early breast cancer (especially node positive) in combination with trastuzumab and chemotherapy, without an increase in cardiac events [36].

3.4.1.3 Cetuximab

Cetuximab, a chimeric mouse/human antibody against the extracellular domain of epidermal growth factor receptor (EGFR), was used in advanced colon/ rectum wild-type RAS gene adenocarcinoma. Pondé et al. found that the predominant cardiac events associated with cetuximab were palpitations (25.8%), chest pain (8.1%), and arrhythmias necessitating treatment (4.8%). The majority of these events were mild and temporary. Troponin dosing and ECG could be sensitive and convenient approaches for the surveillance of these adverse events. [37].

3.4.1.4 Bevacizumab

Bevacizumab, a monoclonal anti-body targeting the vascular endothelial growth factor (VEGF), received approval from the US Food and Drug Administration as the first anti-angiogenesis drug with fluorouracil-based chemotherapy as first-line treatment for metastatic colon/ rectal adenocarcinoma [38]. Inhibition of the protective effects of VEGF on the endothelium could lead to impaired endothelial cell regeneration and subsequent endothelial damage [39]. Clinical trials reported that Bevacizumab use was associated with the following severe adverse events: gastrointestinal (GI) perforations, surgery and wound-healing complications, hemorrhage, non-GI fistula formations, arterial thromboembolism, hypertension, and proteinuria [40]. Al Jazairi et al. showed in their study that among 418 patients treated with bevacizumab, hypertension was the most frequent adverse event, reported in 38 patients (9.1%), followed by thromboembolism reported in 27 patients (6.5%) [41].

3.4.2 Antibody-drug conjugate

3.4.2.1 Ado-Trastuzumab Emtansine (TDM-1)

A novel antibody-drug conjugate called Ado-Trastuzumab Emtansine has been developed. It linked a HER2-targeted monoclonal antibody to a chemotherapy molecule, Emtansine. Emtansine was internalized by the tumor cell, facilitating the delivery of chemotherapy and inducing apoptosis [42]. TDM1 was used for advanced HER2-positive breast cancer. Cardiotoxicity associated with T-DM1 was rare, typically mild, and

reversible, but it had the potential to disrupt treatment continuity [43].

3.4.3 Small molecule inhibitors

Many small molecule inhibitors target multiple tyrosine kinases (TKI) pathways; e.g., Sorafenib, Sunitinib, Axitinib, Pazopanib, Cabozantinib that were vascular endothelial growth factor (VEGF) inhibitors used mainly in metastatic kidney or thyroid cancer [44]. Lung cancer that contained an activating mutation in the epidermal growth factor receptor (EGFR), might be candidate to Afatinib, Erlotinib, Gefitinib, or Osimertinib following the stage of the disease and patient performance status [45]. Another targeted therapies, recently used in hormone receptor-positive/HER2-negative advanced breast cancer, were CDK4/6 inhibitors (CDKI).

3.4.3.1 VEGF TKI

The most frequently reported adverse event during treatment with VEGF inhibitors was hypertension. It typically manifested within hours or days, correlated with dosage, and often resolved upon discontinuation of VEGF inhibitors [46]. The risk was elevated in patients who had pre-existing hypertension or cardiovascular disease, had undergone previous anthracycline treatment, were of advanced age, had a history of smoking, suffered from hyperlipidemia, and/or were obese [47]. Sorafenib and Sunitinib might cause atrial fibrillation [48]. A study based on the Danish healthcare system data set found that CHA2DS2-VASc scores of 0 and 1 in patients with recent cancer were linked with higher risk of stroke/thromboembolism at 2 years than in patients without recent cancer [49]. Treatment with VEGF inhibitors might be complicated by acute arterial events such as aortic dissection, stroke, arterial thrombosis, acute coronary events, and vasospasm, as well as venous thromboembolism (VTE) [50]. A baseline CV risk assessment includes clinical examination, blood pressure measurement, and an ECG with baseline corrected QT interval using Fridericia correction measurement [7].

3.4.3.2 EGFR TKI

In a study involving 123 patients with EGFR-mutant non-small cell lung cancer treated with Osimertinib, a 4.9% incidence of heart failure (HF) or myocardial infarction (MI) was reported. Additionally, there was a significant reduction in left ventricular ejection fraction (LVEF) below 53% in 11% of patients undergoing transthoracic echocardiography (TTE) surveillance [51].

3.4.3.3 Cyclin-dependent kinase inhibitors

Cyclin-dependent kinase-4 and 6 (CDK4/6) were important in the process of cell proliferation. An impairment in CDK4/6-retinoblastoma pathway was involved in breast cancer [52,53]. Cyclins D1, D2 and D3 regulated the CDK4 and CDK6 kinases [54]. Cyclin D1 (CCND1) was a transcriptional target of the estrogen receptor and was overexpressed in about half of breast cancers [53,55]. CDK4/6 inhibitors induced cell cycle arrest in retinoblastoma protein competent cells [56]. Novel therapies such as CDK4/6 inhibitors (CDKI) (monotherapy in conjunction with endocrine therapy) have been the first-line treatment option for patients with hormone receptor-positive/HER2-negative unresecable or metastatic breast cancer [57]. In randomized trials of Ribociclib, it was observed that some patients experienced QT interval prolongation. However, this was reversible and effectively managed by interrupting or reducing the dose, without any noticeable clinical consequences. it was strongly advised to avoid the concurrent administration of Ribociclib with drugs that were recognized to prolong the QT interval [58]. Because of the increased risk of QT prolongation, combining Ribociclib with Tamoxifen (endocrine therapy, see chapter 3.5) was not recommended. Instead, the combination was with an aromatase inhibitor [7].

3.5 Endocrine Therapy

3.5.1 Tamoxifen

The first-generation selective estrogen receptor modulator (SERM), i.e. Tamoxifen, exhibited estrogen-like actions in certain tissues while acting as an antagonist in others. It demonstrated estrogen-like effects on bone alongside antagonist effects on the breast. However, an undesired effect of tamoxifen was its estrogen-like activity on the endometrium [59]. It was used for pre-menopausal hormonereceptor positive breast cancer, especially in the adjuvant setting. The risk of developing thromboembolism (VTE) with Tamoxifen was two to three-fold [60]. In order to determine the safe stoppage and restart times of Tamoxifen before and after surgery, Hussain et al. have considered the pharmacokinetics of the drug. The primary route of excretion for Tamoxifen was through feces, with approximately

65% of the administered dose excreted within a two-week period. Consequently, around 98% of the drug would be completely eliminated from the plasma within three weeks.

After major surgeries such as joint replacement, Tamoxifen was discontinued for three weeks before and after the procedure [61]. This duration was determined based on the surgery's nature (which posed a high risk of VTE) and the rehabilitation duration. Typically, this interruption in Tamoxifen treatment was deemed acceptable without significant risk of cancer progression or recurrence, although conclusive evidence is still lacking [61]. Webster et al. have demonstrated that, compared to patients who did not receive Tamoxifen perioperatively, those who received Tamoxifen did not have an increased risk of thrombotic flap complications after an autologous breast free flap reconstruction surgery [62].

3.5.2 Aromatase inhibitors (AI)

In postmenopausal women, estrogens are synthesized in most of the body compartments, including connective tissue, skin, the liver, and muscle [63]. While circulating androstenedione as well as testosterone in postmenopausal women is considered of adrenal origin, The aromatase is able to convert testosterone into Estradiol (E2) and androstenedione into Estrone (E1) [64]. Aromatase inhibitors blocked this pathway, reducing Estrogen- mediated cancer cell proliferation in hormone receptor-positive breast cancer in the adjuvant or metastatic setting. Aromatase inhibitors showed superiority over Tamoxifen as adjuvant therapy in postmenopausal women [65]. The most common adverse events during AI therapy were menopausal symptoms, and patients were more likely to develop hyperlipidemia, hypercholesterolemia and hypertension, which were known risk factors for cardiovascular disease. Monitoring of these metabolic disorders was mandatory [66].

3.6 Ovarian Function Suppression

Natural or induced menopause, whether intended outcome or inevitably induced by previous therapies (e.g., post-chemotherapy, ovarian ablation), was a common occurrence in women undergoing cancer treatment. In advanced hormone receptor positive breast cancer or at high risk of recurrence, it was considered among the therapeutic strategy. In this subgroup, ovarian function suppression (often with Luteinizing hormone-releasing hormone (LHRH) agonists) was performed in pre-menopausal women in conjunction with targeted therapies and/ or endocrine therapy [8]. Also, Overproduction of free radicals such as reactive oxygen species (ROS), and decreased antioxidant levels could lead to atherosclerosis. This decline, combined with a gradual loss of estrogen in the female reproductive system, was highly associated with the various sequelae of menopause such as heart disease and vasomotor disturbances in addition to non-cardiac effects such as osteoporosis. Managing metabolic changes remained a milestone to prevent severe cardiovascular events [67].

3.7 Anti Androgen Therapy

3.7.1 LHRH agonist

Androgen deprivation therapy (ADT) with LHRH agonist (e.g., Goserelin, Triptorelin) served as the primary treatment for hormone-sensitive prostate cancer, with indications for neoadjuvant or adjuvant treatment in the radiation therapy subgroup, particularly for intermediate and high-risk localized or advanced disease [68]. Measuring serum testosterone level during medical castration was recommended by prostate cancer guidelines to assess its efficacy and define castration resistance [69].

3.7.2 First generation antiandrogens

Bicalutamide, a non-steroidal oral antiandrogen, was approved for use in conjunction with LHRH analogues in men with hormone-treatment-naive prostate cancer, and might be used in clinical practice in metastatic setting [70]. It was recommended to precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients in order to overcome a probable flare in testosterone with initial LHRH agonist alone [70]. According to the TERRAIN, a randomized double blind phase II study, a congestive cardiac failure was reported in 1% of patients treated with bicalutamide in metastatic prostate cancer patients [71].

3.7.3 Second generation antiandrogens

Enzalutamide and Apalutamide were second generation androgen deprivation therapy that might be used in prostate cancer. Enzalutamide inhibited binding of androgens to the androgen receptor, androgen-receptor nuclear

translocation, and androgen-receptor-mediated DNA binding [72]. A grade 3 (following the Common Terminology Criteria for Adverse Events (CTCAE)) cardiac events were reported in 2% of patients who received Enzalutamide in the TERRAIN trial [71].

3.7.4 Third generation antiandrogens

Abiraterone was a selective inhibitor of cytochrome P450 17α-hydroxylase-C17,20 lyase (CYP17A1) that resulted in the inhibition of testicular and adrenal androgen synthesis [73]. The inhibition of CYP17A1 also led to a reduction in cortisol synthesis, accompanied by an increase in the synthesis of deoxycorticosterone, corticosterone, and adrenocorticotropic hormones (ACTH). The addition of corticosteroids (e.g., 10 mg per day of prednisone) to abiraterone acetate allowed this feedback regulation to be stopped (70). Abiraterone was frequently employed treatment for metastatic prostate cancer [74]. A post hoc analysis of the COU-AA-302 trial, which established the efficacy of Abiraterone in chemotherapy-naive patients, showed an increased relative risk of developing cardiac toxicity and hypertension [75].

The correlation between ADT and an increased risk of metabolic syndrome, diabetes, and thus cardiovascular disease with the conjunction of Abiraterone has been firmly established. Abiraterone was approved only for patients who had undergone surgical orchidectomy or were receiving LHRH agonist/antagonist therapy [74].

3.8 Immune Checkpoint Inhibitors (ICI)

Immunotherapy encompasses monoclonal antibodies targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death ligand 1 (PD-L1). These antibodies activated the adaptive immune system against tumor cells by inhibiting negative immune regulation, thereby enhancing antitumor immune responses [42]. The mechanisms of cardiovascular toxicities were not clear. Metabolic perturbations resulting from cytokine release syndrome could contribute to systemic toxicities [76]. The most concerning complications were myocarditis and pericarditis, which have resulted in early and often permanent cessation of the used medication. Corticosteroids and the withdrawal of the culprit treatment were the milestones of events management [77].

In a recent trial involving the checkpoint inhibitor Atezolizumab, myocardial infarction (MI) was documented. In cases where troponin elevation was detected, the differential diagnosis encompassed acute coronary syndrome. The precise cause remained unclear, whether it involved increased atherosclerotic plaque rupture, ICI-triggered coronary vasculitis, or focal myocarditis mistaken for acute MI. Symptoms included chest pain, new ischemic ECG changes (e.g., ST elevation, ST depression, T wave inversion), elevated cardiac troponin levels, and typically new regional wall motion abnormalities on echocardiography or cardiac magnetic resonance imaging (CMR). Coronary angiography served as a diagnostic tool, with percutaneous coronary intervention recommended if a culprit occlusion or severe stenosis was identified [78].

3.9 Radiotherapy

Radiation therapy (RT) is a comprehensive approach in cancer treatment, used in approximately more than 50% of cancer patient treatments in different stages of the disease. Nevertheless, RT administered in the thoracic region, or the left-sided breast cancer, had the potential to impact cardiac function.

Although the risk of cardiac toxicity was influenced by various factors, including the patient's baseline cardiac risk and cardiotoxic systemic therapy, the risk of heart disease and coronary events was projected to increase by 4–7% for each 1 Gy increase in mean dose received by the whole heart (Dmean) [79]. Recently, there has been a notable rise in the use of Intensity-Modulated Radiation Therapy (IMRT) for treating breast carcinoma. This approach yielded a more favorable dose distribution compared to traditional three-dimensional (3D) radiation therapy. Moreover, it resulted in a decreased radiation dose to adjacent healthy organs, particularly the heart and lungs [80,81]. Another technique that might be proposed to the patient undergoing radiotherapy to the left-sided breast cancer or mediastinal lymphoma, was the deep breath hold inspiration. This technique had the advantage of heart sparing from the target volume irradiation [82].

Radio-induced cardiac toxicity encompassed a range of conditions affecting the pericardium, coronary arteries, heart valves, and ventricles, alongside conduction abnormalities and

arrhythmias [83]. These issues arose from decreased capillary density, endothelial cell senescence, accelerated atherosclerosis, and fibrosis, leading to thickening of cardiac walls. Thus, the mean dose to the whole heart was less accurate tool for cardiac complications prediction, and other parameters were explored. A list of pertinent heart subregions that might be delineated for having additional dosimetric parameters (e.g., maximum dose (Dmax), or the volume receiving a specific dose), while potentially not exhaustive, might include the following: coronary arteries, large cavities, great vessels, aortic root encompassing the aortic valve, mitral valve, interventricular septum, left ventricle wall and segments, as well as the sinoatrial and auriculoventricular nodes [83]. Although to be more informative, the delineation of these elements was not frequently reported during radiotherapy planning [84]. Immediate coronary angiography and percutaneous coronary intervention (PCI) were advised for patients experiencing cancer and acute coronary syndrome, provided that the prognosis for cancer was at least 6 months [85]. Another particular situation that might be faced during thoracic radiotherapy planification, was patients with cardiac implantable electronic devices. It was essential to delineate the device and ensure that the total dose delivered to it didn't exceed 5 Gy, ideally aiming for less than 2 Gy. Throughout the treatment session, audio and video monitoring, along with the presence of an onsite emergency physician and rhythmologist were imperative [7].

4. CONCLUSION

The field of cardio-oncology has seen significant expansion due to the rapid advancements in cancer therapies. While these treatments have markedly enhanced survival rates among cancer patients, they also pose risks of cardiovascular and metabolic complications, necessitating a comprehensive and collaborative approach to patient care.

By customizing treatment approaches according to the specific characteristics of the cancer, healthcare providers can optimize therapeutic outcomes while mitigating adverse effects. This integrated care model ensures that cardiovascular risks are managed alongside oncological treatments, enhancing overall patient outcomes.

Further studies are required to elucidate the optimal management of cancer patients with fewer complications, underscoring the importance of continued research and collaboration in this evolving field.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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